REMARKS

Claims 21, 32-54, 56-66, and 68-78 are pending in the present application. Claims 21, 42, 43 and 65 have been amended to more clearly point out certain embodiments of the present invention. Claims 79-82 have been added. Support for the amended claims can be found throughout the specification and the previous claim sets. Support for certain amendments are also provided at the following exemplary locations within the specification: for claims 21, 43 and 65, support for the amendment can be found, *e.g.*, at page 82, line 33 through page 83, line 15; for new claim 79, support can be found, *e.g.*, at page 67, line 14 through page 68, lines 33; for new claim 80, support may be found, *e.g.*, within Examples 2 and 3; for new claim 81, support may be found, *e.g.*, within Example 13, page 84, line 27 through page 86, line 5; for new claim 82, support may be found, *e.g.*, at page 84, lines 17-22. No new matter has been added by these amendments.

Objections to the Specification

The Action has requested an update of status for all parent priority applications. Accordingly, by way of amendment to the cross-reference section of the application, as noted above, Applicants have updated the status of all parent priority applications. Thus, Applicants respectfully submit that this requirement has now been met.

Information Disclosure Statement

The Examiner indicated that the During reference had been considered only to the extent of the previously submitted English translation. Accordingly, Applicants have now obtained a full translation of this document which is included herewith and listed on the accompanying Information Disclosure Statement (PTO Form-1449).

Drawings

Applicants thank the Examiner for noting that the instant application was filed with informal drawings which are acceptable for examination purposes. Accordingly, Applicants will file formal drawings upon allowance of the instant application.

Double Patenting

Claims 21 and 32-78 stand provisionally rejected for obviousness-type double patenting as being unpatentable over claims 21-30 and 36-37 of co-pending U.S. Application No. 09/199,534. The Action states that although the claims are not identical, they are not patentably distinct because the claims of the instant application allow for the inclusion of a leader sequence as in 09/199,534. Furthermore, it would have been obvious to utilize the methods set forth in claims 36-37 of the 09/199,534 application to make the claimed product since the method simply introduces the nucleotides containing the gene of interest into the claimed transgenic plant, and thus would not be patentably distinct from the transgenic plant.

Applicants respectfully traverse this ground for rejection. Without acquiescing to this ground of rejection and solely in order to facilitate prosecution, a Terminal Disclaimer is filed herewith to obviate this ground of rejection.

Claims 21 and 32-78 stand provisionally rejected for obviousness-type double patenting as being unpatentable over claims 21-64 of co-pending U.S. Application No. 09/512,568. The Action states that although the conflicting claims are not identical, they are not patentably distinct from each other because immunoglobulin and antibodies are prototypic and main species of multimeric proteins.

Again, Applicants respectfully disagree and traverse this ground for rejection. However, without acquiescing to this ground of rejection and solely in order to facilitate prosecution, a Terminal Disclaimer is filed herewith to obviate this ground of rejection.

Claims 21 and 32-78 stand rejected for obviousness-type double patenting as being allegedly unpatentable over claims 6-12 of U.S. Patent No. 5,959,177. The Action alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because of the genus-species relationship. Thus, the Action concludes, the scope of the claims of the instant application is rendered obvious by the patented claims.

Claims 21 and 32-78 stand rejected for obviousness-type double patenting as being allegedly unpatentable over claims 1-5 of U.S. Patent No. 5,202,422. The action alleges that the conflicting claims are not identical, they are not patentably distinct from each other because immunoglobulins are the prototypic and main species of glycopeptide multimeric proteins which are used to induce passive immunity.

With respect to the double patenting rejections noted above for U.S. Patent Nos. 5,959,177 and 5,202,422, Applicants respectfully disagree and traverse these grounds for rejection. However, in order to facilitate prosecution without acquiescing to these rejections, Applicants have included herewith a fully executed Terminal Disclaimer. Accordingly, this rejection has now been overcome.

Rejections Under 35 U.S.C. 112, second paragraph

Claims 42, 55, and 67 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, the Action asserts that in claim 42, the term "the multimeric protein" lacks antecedent basis. With respect to claims 55 and 67, the Action objects to the phrase "one-half of an immunoglobulin molecule" as unclear.

Applicants thank the Examiner for noting these issues of clarity. Accordingly, Applicants have amended claim 42 to refer to the "immunoglobulin product" rather than the "multimeric protein" thereby obviating the rejection based upon antecedent basis. Claims 55 and 67 have been canceled, without prejudice, as it is believed that other claims related to portions of antibodies adequately encompass the scope of these claims. Nevertheless, it is submitted that one of ordinary skill in the art could readily determine what the term "one-half of an immunoglobulin molecule" would encompass. In this regard, Applicants rely on the use of these terms in the art. In other words, Applicants submit that "one-half of an immunoglobulin molecule" encompasses "one-half" be it the top, the bottom or either side without limitation, so long as those of skill in the art would term the immunoglobulin molecule as being one-half of the native form. Accordingly, Applicants reserve the right to pursue such claims in a timely filed continuation application.

As the above grounds of rejection have now been addressed, Applicants respectfully request their withdrawal.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 21, 32-39, 42-47, 49-57, 60-68, 70-75, and 78 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by During (Doctoral Dissertation). The Action asserts that During teaches a transgenic tobacco plant comprising cells which contain and express nucleotide sequences encoding immunoglobulin heavy and light chains of an anti-NP-IgM antibody, at least one of which contains a leader sequence from the α-amylase gene of barley. Further, the Action asserts that the antibody was glycosylated and that the antibody would inherently contain a paratope.

Applicants respectfully traverse this ground for rejection. As an initial matter, Applicants urge that the cited Dissertation does not anticipate the claimed invention as it fails to disclose transgenic plants including the claimed nucleotide sequences or the immunoglobulin products generated thereby. Further, the currently pending claims recite differences that clearly distinguish them from the During art, including, *e.g.*, the requirement for cleavage of the leader sequence. In addition, the cited Dissertation does not meet the requirements of 35 U.S.C. § 102(b), largely because it fails to provide an enabling disclosure.

The Court of Appeals for the Federal Circuit has repeatedly recognized that anticipation requires that each and every element of the claimed invention be disclosed in the prior art reference and that the prior art reference be enabling, thus placing allegedly disclosed matter in the possession of the public. (*See, e.g., Akzo N.V. v. U.S. International Trade Commission*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986), *certiorari denied*, 107 S. Ct. 2470, 96 L. Ed. 2d 382; *also see Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986).)

While During, in his Dissertation, claims to introduce and express both a heavy chain and a light chain in a plant cell, support for such a claim is equivocal at best, as discussed further below. In fact, a close review of the During Dissertation reveals that absolutely no data is presented which unquestionably supports a conclusion that assembled, functional immunoglobulin products are present in the plant cells.

Absent any demonstrated support, one of skill in the relevant art cannot reasonably conclude that antibody assembly occurred. For example, the antibody used in

During's efforts to confirm the presence of an assembled immunoglobulin, which antibody is identified in the Dissertation as "Ac 38", is an uncharacterized antibody with respect to the specific experiments employed in the Dissertation. There is no corroborating evidence in the thesis to establish the ability of the antibody to specifically bind an assembled immunoglobulin molecule. Moreover, it is significant that the characterization of this antibody with respect to its use in the Dissertation has yet to be described in a refereed journal. Ac 38 is an anti-idotypic antibody that has been extensively used as an immunogen in numerous immunology experiments dating to the early 1980s. There is no report addressing the ability of this antibody to detect B 1-8 after the fixation and denaturation procedures prior to the immunogold labeling experiments described in the Dissertation. During emphasizes that the Ac 38 antibody requires the correct tertiary and quaternary procedure to bind B 1-8 (p. 25). These structural requirements are destroyed by fixation (*See, e.g.*, page 25 of the During Dissertation, wherein antibody Ac 38 is simply identified as being "donated by A. Radbruch"). The During Dissertation also contains a substantial amount of discussion regarding expression levels and the need for extremely sensitive assays to determine whether any antibodies are even expressed, which calls the entire project into question. This discussion includes statements indicating that detection was at the limits of immuno-detetection and that suspect antibody had to be affinity purified from leaf extracts prior to any attempt at detection (page 31), further at both page 31 and page 60, During indicates that heavy chain was undetectable (top p. 34, para 1 and 2) and light chain is located in the cytoplasm (bottom p. 35) whereas "aggregated" antibody is also located in the chloroplast. The precise characteristics of an "aggregated" antibody are undefined and likely the result of aggregation of light chains and not assembled heavy and light chains given the lack of ability to detect heavy chains. (page 35) (page numbers of the Dissertation noted above are based on the previously submitted version of the thesis and not the fully translated version submitted herewith).

Further, when discussing the arrangement of the light chain and marker genes under the expression of a dual promoter, During freely admits that "the values for the double promoter do not agree with already-known values and those measured in this work in enzyme tests" on page 47 and that further experimentation in which "[a] systematic, detailed investigation is necessary with a construction that allows both directions in a plant to be analyzed and correlated" on page 46 is required to conclusively demonstrate expression from the dual

promoter. Between the lack of appropriate controls in the experiments described by During and his frequent admissions that his data are limited and inconclusive, one of skill in the art will appreciate that During's "findings" are suspect.

The data presented in the During Dissertation are also highly suspect in that they suggest sequestration of antibody within a chloroplast; such an observation is not consistent with the known behavior and function of signal sequences, nor are the results consistent with those obtained with the same signal sequence fused to lysozyme in the same study. Even During had no explanation for this unexpected anomaly (see, *e.g.,* page 57, previously cited translation), and he conceded that further experimentation would be required before he could even attempt to address this inconsistent behavior. Further statements by During that "[a] correlation of the observed signal intensities in immunogold labeling with promoter activities cannot be determined from the available data" (see pages 58-59) and that "one must wait for statistical reinforcement of this result" (see page 62) illustrate During's own uncertainty when discussing the alleged detection of assembled heterodimeric antibody. Moreover, no gold particles are found associated with the cell wall leading one to believe that no functional secretion signal or other processing event is present. The absence of immunoglobulin association with either Golgi or cell wall is confirmed by During's evaluation of his data (see fully translated version, page 112, last sentence bridging pages 112-113).

Thus, contrary to the claims made in the "discussion section" of the During Dssertation, the data do not verifiably support a conclusion that the heavy and light chain DNA sequences were stably integrated into the plant genome, that both heavy and light chains were expressed, that assembly of the heavy and light chain occurred, or that such assembly produced a functional, biologically active immunoglobulin product. Thus, the During Dissertation clearly reaffirms Applicants' finding that individuals of skill in the art had not recognized and solved the problems addressed and overcome by the present invention.

Moreover, as noted above, rather than anticipating the present invention, During affirmatively teaches away from the present invention. In particular, given the teachings of During no one of skill in the art would have been motivated to attempt such antibody production given the infinitesimal quantities stated to be produced.

Therefore, for all the foregoing reasons, Applicants respectfully submit that these grounds of rejection have been overcome and thus request their withdrawal.

Claim Rejections Under 35 U.S.C. § 102(e)

Claims 21, 32-40, 42-47, 49-58, 60-68, 70-76, and 78 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Goodman (U.S. Patent No. 4,956,282). In particular, the Action alleges that Goodman teaches transformation of monocots and dicots by introducing a vector containing nucleotide sequences encoding immunoglobulin heavy and light chains for expressing immunoglobulins and heterologous leader sequences to direct the expressed product to a particular organelle into plant cells and culturing them. Moreover, the Action concludes that the antibody would inherently contain a paratope and that the antibody of Goodman appears to be glycosylated and free of sialic acid.

Applicants respectfully traverse this ground for rejection and submit that the currently claimed invention is clearly not anticipated by Goodman. It is well supported tenet of patent law, that a reference cannot anticipate a claim unless it sets forth each and every limitation of the claimed subject matter. Further, in order to be useable as prior art at all, the reference must be enabled for that which it is relied upon to teach. With this in mind, Applicants respectfully submit that Goodman is neither enabled for the broad teaching the Examiner accords it nor does Goodman teach each and every element of the claimed invention.

The Action alleges that the Goodman reference describes a plant expression vector for producing structural genes of interest, including "***immunoglobulins, with the structural genes coding for the light and heavy chains and desirably assembly occurring in the plant cell***" (See column 3, lines 20-23). However, within the entire specification of Goodman, there is no other discussion of immunoglobulins. Rather, Goodman expresses a single chain polypeptide in a plant cell, but does not describe the expression and assembly of any immunoglobulin products. In other words, the Goodman reference speculates by the single above-quoted sentence that immunoglobulin heavy and light chains could be expressed and assembled in a plant cell. At best Goodman provides an invitation to experiment and does not teach appropriate cleavable leader sequences.

In other words, contrary to the assertions of the Action, Goodman does not provide "sufficient guidance to enable one skilled in the art to use the methods for the production of immunoglobulins" because Goodman does not describe procedures for production of any immunoglobulin product at all. Goodman is unaware of requirements for production of immunoglobulin products in plants and Goodman is silent on this point. Thus, it cannot be said that Goodman provides any guidance whatsoever to solve the particular problem of expression and assembly of immunoglobulin products in plants.

It is pertinent to note that the specification of the Goodman patent has been interpreted relatively narrowly with respect to enablement. In the case *In re Goodman*, 29 U.S.P.Q.2nd 2010, 2013 (Fed. Cir. 1993), the Federal Circuit opined upon the disclosure of a continuation of the herein cited patent and noted that "Goodman's specification contains a single example of producing gamma-interferon in the dicotyledonous species, tobacco. This single example, however, does not enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell." Accordingly, the breadth of enablement accorded Goodman by the Examiner is inconsistent with its judicial interpretation and thus this reference should not be viewed as teaching anything in particular with respect to production of immunglobulins in plants.

Even assuming, *arguendo*, that Goodman is enabled for all that it allegedly teaches, Goodman remains deficient in that it does not teach each nucleotide sequence encoding an immunoglobulin polypeptide having a leader sequence forming a secretion signal that is cleaved from the immunoglobulin polypeptide following proteolytic processing. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 21 and 32-78 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over During.

Applicants respectfully traverse this ground for rejection. As noted above, During suffers from many deficiencies including, for example, cleavage site ambiguity in the leader sequence being a consequence of the During strategy. The leader sequence strategy used by During did not result in experimental success and the During results as a whole are discouraging

as During himself indicates by noting: (i) very low levels of accumulation, page 30 and 67, (ii) no detection of heavy chain, page 60, (iii) immunoglobulin accumulated in the cytoplasm, page 35, (iv) absence of direct evidence for assembly, page 35, (v) inefficient assembly by indirect measurement, page 35, and (vi) predominant accumulation in chloroplasts, page 62 (page references refer to previous and partially translated version of the Dissertation). Moreover, plant cell secretion is not observed as no association of antibody with the cell wall is observed. Accordingly, those of skill in the art would not have recognized the During strategy as providing reasonable commercial applicability and in fact, During teaches away from the presently claimed plants and methodology for production of immunoglobulin products in plants as the results of During are questionable at best. Furthermore, During clearly does not teach or suggest any functional leader sequence that is cleaved following proteolytic processing and neither During nor the art at the time suggest how one would create such a functional leader/secretion sequence in a plant cell.

In addition, the Action asserts that production of an antibody or abzyme by the During strategy would be obvious and without any surprising or unexpected results. This assertion completely ignores the contrasting nature of the results obtained by During and those obtained by the present inventors. During struggled to obtain immunologically detectable levels of expression, noting:

"A method therefore had to be developed that permits the sought protein to be enriched from the crude extract before Western blot or preferably to be isolated and concentrated to detectable concentrations" (page 87, last full paragraph)

"By direct Western blotting from the crude extract of calli or induced plant material, only unsatisfactory results can be achieved" (page 89, first sentence of first full paragraph)

"The difficult reproducibility of biological material is particularly clear in these analyses, precisely when inductions are carried out. The total found amounts of antibody protein lies in the lowermost range of the detection limits and therefore form only a very limited fraction of the total protein of the transformed plants." (page 89, last full paragraph) (All Page numbers used in the discussion immediately above are based upon the fully translated version of the During Dissertation submitted herewith).

Contrary to the ineffective strategy set forth by During the present inventors achieve clearly detectable levels of immunglobulins in crude extracts. For example, representative expression of 200 to 500 micrograms of SIgA-G per gram of plant material (See, *e.g.*, instant specification page 99, lines 22-23) and 2 to 1400 ng/mg of plant protein for IgG chains (See, *e.g.*, instant specification page 68, lines 15-26) is evidenced by the instant specification.

The unexpected and surprising results of using plants to process, assemble, and secrete immunoglobulin products by the methods set forth in the present application is not only supported by the instant specification and the prior art, but also by the fact that the results were so surprising that the present inventor's work was featured on the cover of the prestigious journal Nature (Nov 2;342(6245):76-78, 1989).

Accordingly, given the above remarks, it is clear that not only does During lack an enabling disclosure and teach away from the present invention, but the results obtained by the present inventors were clearly unexpected and surprising to the scientific community, especially in light of the lack of success demonstrated by During.

Rejections Under 35 U.S.C. § 103(a)

Claims 21 and 32-78 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Goodman (U.S. Patent No. 4,956,282). In particular, the Action asserts that while Goodman does not teach transformation of algae, such transformation would have been well within the means of one of ordinary skill in the art. Further, the Action alleges that while the antibody of Goodman generically does not have catalytic activity (abzyme), it would have been obvious to transform plants using the method of Goodman to express another desired antibody, such as abzymes of the prior art, without any surprising or unexpected results.

Applicants respectfully traverse this ground for rejection and submit that the presently claimed invention was in fact so surprising that the results graced the cover of the prestigious Journal Nature (Nature Nov 2;342(6245):76-78, 1989).

Applicants respectfully traverse this ground for rejection and submit that at best, the Goodman reference provides a suggestion to try to produce immunoglobulin products in a plant cell. The general deficiencies of Goodman including the finding by the Federal Circuit that

the Goodman specification provides very limited enablement was discussed in greater detail above and thus will not be repeated here. However, given the discussion above, the assertion that it would be obvious to use the disclosures of Goodman to arrive at Applicant's invention is nothing more than an "obvious to try" standard. This standard has continuously been determined by the courts to be an improper basis for rejection under 35 U.S.C. § 103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

It is evident upon review of the presently pending claims that the invention requires both the presence of encoding nucleotide sequences and biologically active products of such expression. In other words, the invention requires not only expression of the immunoglobulin molecules, but also correct post-expression processing so as to produce a biologically active protein. As is evidenced in the Office Action mailed May 26, 1999 Goodman may at most be only arguably viewed as teaching the expression of non-multimeric proteins in plant cells, not multimeric proteins. Again, the only discussion of immunoglobulins at all in the text of Goodman occurs at column 3, lines 20-23, stating:

> Structural genes of interest include α-, β- and γ- interferons, immunoglobulins, with the structural genes coding for the light and heavy chains and desirably assembly occurring in the plant cell, lymphokines... (emphasis added)

The use of the phrase "desirably assembly occurring" clearly indicates the speculative nature of immunoglobulin expression in plant cells and indicates that correct post expression assembly of such an immunoglobulin is unknown and a mere desire or hope at best. Such explicit speculation cannot support an obviousness-type rejection.

As Applicants believe that all grounds for rejection have now been obviated, Applicants respectfully request that the Examiner withdraw the same.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Applicants respectfully submit that all of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is encouraged to contact the undersigned at 206-622-4900 if she has any questions.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:rap

Enclosures:

- Return Receipt Postcard
- Transmittal Form
- Fee Transmittal Form
- Petition for an Extension of Time (+copy)
- Terminal Disclaimers (2)
- During Thesis (German)
- Information Disclosure Statement
- Form 1449
- Cited Reference (English Translation of During Thesis)

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Version with Markings to Show Changes Made

In the Specification:

Please amend the specification by replacing the existing cross-reference section at page 1, line 5 with the following:

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. Application No. 08/642,406, filed May 3, 1996, which issued as U.S. Patent No. 5,959,177 on September 28, 1999; which application [This] is a continuation-in-part of [USSN] U.S. Application No. 07/971,951, filed November 5, 1992, which issued as U.S. Patent No. 5,639,947 on June 17, 1997; which application is a continuation of [USSN] U.S. Application No. 07/591,823, filed October 2, 1990 [(now U.S. Patent No. 5,202,422)] , which issued as U.S. Patent No. 5,202,422 on April 13, 1993; which application is a continuation-in-part of [USSN] U.S. Application No. 07/427,765, filed October 27, 1989 [(abandoned] and now abandoned; the disclosures of which are incorporated by reference herein.

In the Claims:

Please cancel claims 55 and 67 without prejudice.

Please amend the claims as follows:

21. (Twice Amended) A plant, comprising:

(a) plant cells containing nucleotide sequences encoding one or more biologically functional immunoglobulin product not normally produced by the plant; and

(b) biologically functional immunoglobulin product encoded by said nucleotide sequences, wherein each nucleotide sequence encoding an immunoglobulin polypeptide encodes a leader sequence forming a secretion signal that is cleaved from said immunoglobulin polypeptide following proteolytic processing.

42. (Amended) The plant of claim 21, wherein the [multimeric protein] immunoglobulin product includes a J chain.

43. (Amended) A plant, comprising:

(a) plant cells containing nucleotide sequences encoding an immunoglobulin product containing at least a portion of an immunoglobulin heavy chain polypeptide, wherein said polypeptide further comprises a leader sequence forming a secretion signal; and

(b) biologically functional immunoglobulin product encoded by said nucleotide sequences, wherein said leader sequence is cleaved from said heavy chain polypeptide following proteolytic processing.

65. A plant, comprising:

(a) plant cells containing nucleotide sequences encoding an immunoglobulin product containing at least a portion of an immunoglobulin light chain polypeptide, wherein said polypeptide further comprises a leader sequence forming a secretion signal; and

(b) biologically functional immunoglobulin product encoded by said nucleotide sequences, wherein said leader sequence is cleaved from said heavy chain polypeptide following proteolytic processing.